**Among of host of CRISPR-related advancements, researchers at NIH are moving closer to drug trials for SPG3A and SPG15**

Q&A with Dr. Craig Blackstone, M.D., Ph.D., a Senior Investigator at the National Institute of Neurological Disorders and Stroke at the National Institutes of Health in Washington, D.C.

Dr. Blackstone is a leading HSP researcher whose laboratory investigates the cellular and molecular mechanisms underlying hereditary movement disorders.

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**Dr. Craig Blackstone has been working for years to unravel the mysteries of HSP with the goal of finding a treatment. His lab at the NIH conducts basic research into how HSPs work, the pathology of the disease, so they can begin to test potential therapies.**

**In just the past few years, Dr. Blackstone and his team have moved beyond understanding the pathology to now identifying small molecules that might work to arrest and, possibly, reverse symptoms in some patients.**

**What follows is a discussion of the important work Dr. Blackstone is doing in his lab and, more broadly, how HSP research has progressed since our last conversation in the late winter of 2016.**

**Allen:** Hi Craig. Thank you again for making the time for our call.

**Craig:** Oh, no problem at all.

**Allen:** Last time we talked you were talking about doing an assay for SPG3A. Has that moved forward?

**Craig:** We're still doing some actuallyworking in this area. One thing we've done with our mouse models is we made [the symptoms] more severe. And the reason we do that is … we want to push the model system. We want to get the micem to have enough of a phenotype that we can see if they respond to therapy. So we've created a mouse that has a very severe phenotype by mutating several related HSP genes, and it's spasticity and we can see it and now we're trying our first drug trial.

**Allen:** What is the name of the drug?

**Craig:** It's a member of the epothilones; there is ~~, there's~~ a whole ~~class~~ family of these drugs. We're trying one of them that has good brain penetration when given systemically.
~~They were used in cancer for many years. They still are. It's one that's improved spinal cord injury in mouse models.~~ If it looks safe, and if it looks like it's having enough efficacy, then you start to think ~~about~~ 'Well, can we try it in a small human trial to see whether~~if~~ it's safe?'
And, in this case, it will be good because it's been given to people before. And we ~~know what doses it's been given at because it's been tested for cancer.~~ at least have a started point for how to dose based on previous cancer studies.

**Allen: When do you think you will have results?**

**Craig:** Well, in our mice we would know probably within a year to a year and a half. If there's absolutely no concerns, ~~and you've got this great data,~~ then within a few years, then you ~~would start~~ could consider a small trial in~~of~~ patients.

**Allen:** You've always been very confident about the ability of science to find an answer to the HSPs? Do you still believe that?

**Craig:** ~~Well,~~Yes, I still do~~., And the reason I do partly is not just because I'm a neurologist but it's~~ because there's many examples in other diseases~~ cancer. I mean if you see the~~ For instance, cancer treatment is being transformed by advances in immunotherapy~~ and things like that~~, ~~I mean~~and those advances are based on a molecular understanding of the cancer. In neurologic disorders like spinal muscular atrophy, there have also been dramatic new treatments based on our understanding of disease pathogenesis.

In a sense, what we're ~~not~~ doing ~~that~~ is not much different~~ly~~. We're trying to understand the very fundamental basis of ~~our disease~~HSPs ~~and we're trying to intervene on it~~so we can have targets to intervene. I think that we've seen enough examples in other disorders where that's worked. ~~And that's the reason I'm so enthusiastic about this – we're doing essentially the same thing.~~

And genetics has been one of the keys. Remember, it's ~~that's something that's~~ relatively recent that we could ~~get~~ obtain this genetic information so quickly. So that's another reason~~why~~ I'm so optimistic~~confident~~. We have new tools that we didn't have before. ~~And we have examples from other disorders that have been clearly successful including some neurologic disorders and, when you combine all that, it makes me optimistic.~~

**Allen:** That's great news, Craig. Very exciting. I also wanted to talk about the state of research in general today, if that's okay?

**Craig**: Sure.

**Allen**: Specifically, I wanted to start off with gene-editing. I did some basic research by typing "gene-editing" into Google this morning and there is headline after headline about the gene- editing technology CRISPR. It's getting more precise, you know, down to the point where a single letter in a gene can be edited out and replaced successfully.

So I wanted to get your take on these headlines because, as a lay person, you read these things and you think, "Wow, a treatment is just around the corner." But, as far as actually advancing a treatment, what are these headlines saying to you?

**Craig:** I think it's incredibly exciting, and as we know more and more about CRISPR and gene editing, it's getting safer all the time. But, like most scientists, the first thing you think about is well, 'What could possibly go wrong? Are there off-target effects? Is it really going to be just as simple when you get into an in-vivo [i.e., in a living being]? Are Is there going to be any serious adverse effects to it?' When a technology's new there's no adverse effects since it hasn't it often hasn't been around been around long enough to understand possible adverse effects fully. But as time goes on what will we start to see?

So that's one issue. But certainly the idea is very attractive. I mean you go in and you fix the basic cause of the disease … in theory, it should not progress anymore past then, and you might even get improvement from what you had been before.

But it brings up a couple of other points: The first one would be when do you have to do is the best time to do this? Like, let's say we could go in and edit a new gene anytime we wanted to. Well, do we have to do it right when somebody's born or could we do it in somebody who's olderwait? If so, would they still get the same types of benefits? So, a lot of it is like any therapy: When do you apply it? When can you do it safely? When can you do it and still get the maximum effectiveness without having a huge amount ofsignificant risk?

WNow, with the nervous system we have another issue, and that's how do you get it delivered to the right cells efficiently. The brain is made of a very large number of neurons that develop in a certain pattern through early life all throughout development. But let's say we have a 10-year-old and we try to deliver a gene and do this gene repairfix through CRISPR, how do we know we can get it enough cells to have meaningful improvement? We don't know yet.

TAnd that's something that we'll eventually learn, but that's it's also a big issue with neurologic therapeutics in general: How do we get our treatmentsthem into the brain? So that's the biggest challenge for something like CRISPR. And, I do agree with you, I think it has a potentially great likelihood ofmany of our therapies can succeeding if we can get themit to the right cells, and enough of those cells, without any adverse effects and get it to enough of those cells.

TBut there's also going to be a lot of experience in this relatively soon. So, if there are barriers, people are going to be working on them very hard.

**Allen:** I see a lot of work in China, other countries. CRISPR is a worldwide phenomenon when it comes to biotech. In China they're using it to treat cancer, build designer dogs. It seems to me that there would be a lot of spill over from this work to address how we can do it in HSP.

**Craig:** We will get expertise from cancer because in cancer, of course, you can just take the blood different types of cells out of somebodya patient's blood or bone marrow, engineer them, and put them back in;, and they circulate throughout your body and do their work. So cancer is where a lot of these things are going to be tested early on because you can access the cancer or access the cells that you need to very easily. And that's why immunotherapy and all these things for cancer have developed so fast.

Again, our biggest challenge is how do we get our tools therapies to the cells that are affected in the disease, and in what amounts? If we get it to five percent of cells is that enough? Is 10 percent? Over time, we'll learn the answers to those questions. That kind of thing is being done already in terms of in various model systems. I think we will get that kind of information relatively quickly.

Our hope is that if we go early enough with the therapy that we'll prevent a lot of the damage, and we'll prevent the disease from really taking hold. But there is all these issues that even if you replace the a missing protein or let's say you fix the genetic defect, is that enough at that time to prevent worsening of the disease or to restore function? We really hopeThe thing we hope to be able to improve symptoms and stope progression. for most is to have all the symptoms be reversed.

**Allen:** We've talked about this many times in the past about HSP being an "indicator disease"; a disease that opens the doors to a lot of understanding of other central nervous system disorders, right?

**Craig:** Yeah, because the upper motor neurons are so long that any other diseases of

motor neurons or other types of long neurons may benefit from insights into the HSPs~~; it could potentially open the door to us understanding those as well.~~

**Allen:** Are you seeing that? We've talked about that now for eight years. Are you seeing proof of that?

**Craig:** Well, in peripheral neuropathies there are ~~a lot of thos~~examples~~e~~. The~~y're neuropathies of~~se affect peripheral nerves~~,~~ but they're also very long nerves. ~~There's definitely some overlap.~~ Some of the same genes that cause HSP can give rise to peripheral neuropathies. ~~So, in that regard, yes.~~

In terms of other diseases, I don't know for sure. There are ~~I mean there's a~~ lot of diseases that overlap partly with some of the symptoms that you'd see in HSP. Spinal cord injur~~yies certainly does or~~and ALS ~~ALS~~ have~~s~~ certain overlapping features~~. of it that would have a lot of other ones as well.~~

**Allen:** What about multiple sclerosis?

**Craig:** M~~In m~~ultiple sclerosis ~~it might be~~can have symptom overlap, but it's ~~more of~~ an auto-immune or inflammatory type~~kind~~ of disorder. So it's a ~~little bit~~ different disease even though certainly you can damage the same cells through multiple sclerosis.

There's been some very good developments in terms of therapies for MS~~that~~. What we ~~do~~ learn from MS is that when you do treat people with these medicines you change the disease course and that's a great example ~~[~~for~~of~~ how treatments for neurological disorders are progressing~~]~~. Certainly~~,~~ some of the newer developments in spinal muscular atrophy (SMA) are ~~the same way~~similarly exciting. ~~Those types of studies are very encouraging to all of us because~~ W~~w~~e know that it's possible for HSPs as well.

**Allen:** There was a big study that had some very good results here in Columbus at Nationwide Children's Hospital.

**Craig:** Exactly, ~~that was where it was pioneered;~~ amazing recoveries~~y~~ for patients with SMA, a~~. A~~nd that encourages us all. As we ar~~-~~e better able to link different type~~-~~s of HSPs by their clinical ~~cial~~ manifestations and underlying etiologies, we will have compelling targets for therapies.~~As we learn more about the pathways the disease takes; like if you think about SPG11 and 15, we showed a number of years ago there are specific abnormalities in lysosomes. Well, lysosomes are an organelle in the cell and they're also being implicated in things like Parkinson's disease. And our patients actually often have mild to moderate Parkinson symptoms.~~

We always suspected that there would be [cross over] ... and where they meet is hopefully where we identify good therapeutic targets for us to work on. But the advantage, of course, is that there's more money in Parkinson's, a lot more, and their advances might be useful for us as well.

It's important to remember that as you try to link this to other diseases that the vast majority of HSP proteins are not only expressed in the nervous system. They're expressed in cells throughout your body. So the thought is that there's probably a lot of other manifestations outside the nervous system that we know about [that could be linked back to HSP]. And I would expect some to potentially have roles in other types of disorders as well.

**Kommenterede [1]:**
Should this read "don't know about"?

**Kommenterede [2]:**
Yes?

**Allen:** Now, when you say "manifestation", what do you mean?

**Craig:** Symptoms or other diagnostic findings. If you think about all the different HSPs, you've got this laundry list of disorders. Just as an example, in SPG23 there are pigmentary changes in the skin. SPG25 has, for reasons we don't understand, they have disc herniations that you'd get in your back.

So there are some features that are coming up in certain HSPs that we don't 100 percent understand but again it's important to remember these are proteins that often are expressed in a lot of places. In some cases, they may not cause any meaningful problems, so they wouldn't come to medical attention. But you'd say, 'Well, why should we care then?'

Well, one reason is that those can be good biomarkers to follow things to follow like [biomarkers] for therapy because they're easier to access. TYou know, the brain is so hard to access in terms of following things changes in response to for therapy, but if there's a change in your blood cholesterol or something easy to measure, then we could easily use that as a biomarker of disease.

**Allen:** Interesting. So how does that help you move closer to a treatment?

**Craig:** Well, again, we have these 80 genes or so and there are's very few diseases that have this many known genes. , and We're starting to see them coalesce around certain cellular pathways [in the cell]. And some of those pathways are related to other diseases. When we start to see that, that is what moves us closer to therapy. WNow, we can begin to target them [for drug development].

Usually, at the beginning, we're just trying to correct the cell defect -- like an abnormality in lysosomes; we want to correct that but then we want to see, . Then, going up the

ladder, does it do the same thing to a neuron? Does it do the same thing in a mouse model or a fly model? And, then, does it ~~do the same thing~~ ultimately work in a person?

So there's ~~sort of this sort of~~this early pre-clinical development stage~~,~~ but as you know it gets more and more expensive the farther along you go. So you want to have good ideas to start with. And, again, the more convergence you have around the pathway ~~[~~of the disease~~]~~, the more confident you are to ~~spend resources there because you can't do them all.~~ devote additional resources.

**Allen:** Since you bring it up, this seems like a good place to talk about funding. You just got some certainty in this 2018 budget from Congress, right?

**Craig:** ~~I don't know if it's officially approved but there's certainly a path and~~ Yes, there's a desire to fund NIH to a very certain level, which is good because, as you know, uncertainty is hard. If you don't know you're going to have money, you ~~won't~~ might not try to do the experiment.

You don't want to make commitments that you can't meet. So longer-term ~~sort of~~ funding commitments are very important for us. I think there's more certainty now than there has been in the last six months~~., where every three weeks or whatever we're having to prepare to shut down. I mean that's not very efficient.~~

**Allen:** So, with this new funding certainty, are you able to continue to attract top talent?

**Craig:** In terms of getting people to work in the lab? Absolutely. T~~, T~~here is a very large number of young people that want to be physician-scientists ~~that want to~~ and work on disease. We get hundreds and hundreds of applicants each year from people that want to work in the summer or take a year after college.

One of the advantages of being in the U.S., at the NIH~~,~~ in particular, is we can draw talent from all over the world. ~~We can draw talent from schools like Peking University or Seoul National University or, you know, University of Tokyo. These are schools that are far, far more competitive to get into than Harvard or Yale or Princeton.~~

So we have no problem drawing really talented people. A~~nd also one~~nother thing about medicine that's changing is it's increasingly drawing~~a lot of~~ different types of people. Before it was mostly biology ~~majors~~ or chemistry majors, but now you're bringing in computer scientists, physicists, mathematicians -- there's a lot of computational work that's being done. And many of the people in those areas seem quite interested in applying what they know to studies of disease.

So there's no doubt there's a lot of interest among people that are at the early stages of their career throughout the world ~~in doing this~~. O~~That's o~~ne of the things that people worry about when the funding is ~~bad~~ more challenging is that we'll lose a generation of th~~e~~~~o~~se people. You ~~know you~~ don't want to have them say, "Well, I'm not going to do this." And then go off and do something else. Once they do that, you'll never get them back. So I think that's another reason for we're encouraged by ~~at least~~ consistent funding~~, even though we understand things can't go up forever~~.

**Allen:** Do you have enough money in your lab right now to do what you want to do?

**Craig:** I think we have enough, though of course if~~. If~~ we had more, we~~I~~ could always do more. But w~~W~~e're quite well-funded certainly compared to other countries and even compared to many laboratories in the United States. The NIH ~~is very generous. They~~provides ~~give~~ us with a lot of resources.

As you may know there's a couple of small HSP-related foundations now that are specifically trying to develop gene therapies. Now, some of that research can be very expensive. And if these foundations can fund these efforts ~~kick that money in~~, that ~~probably jump starts~~ can jump-start progress pretty dramatically.

**Allen:** Okay, good to know. So, overall, where are we along the spectrum of research-to-treatment compared to where we were eight years ago?

**Craig:** Well, we have identified more genes, right? So I think the genetic part has been very successful. We have ~~all these~~ potential targets ~~on what to approach~~to guide our studies. And out of that process will come compounds and ideas for drugs. One example is SPG5. They know exactly the enzyme that's involved. They can check its effects~~it~~ in the blood and see the abnormality. And they're already starting to give drugs that can, at least in some systems, reverse the problem. So you're going to start seeing more and more examples of that where you're moving closer to therapies because now you know what your target is.

**Allen:** Isn't that about where we were a year ago?

**Craig:** ~~What's happened is t~~They are farther along that path. And there's a lot of people starting to try different types of therapies. ~~So I think it's happening more.~~ I~~Now, i~~t was happening a little bit eight years ago, too, but it's happening more now. You're starting to see early phase human trials or certainly therapeutic trials in organisms that are clearly directed more toward the goal of therapy than maybe toward the goal of understanding ~~[~~the disease~~]~~.

The other big change, of course, is CRISPR and the possibility of gene editing. So we're starting to see more and more diseases where ~~you're going in and directly~~ther~~-e~~ is the option to go in and directly change~~ing~~ the gene. O~~Now, o~~f course, that's new. That wasn't something you couldn't do years ago or even couldn't contemplate. That's really been a recent advancement.

At this point in the HSPs, we're starting to get enough ideas of what type of drugs we want to deliver. So the delivery methods are going to become more important: Do we use viruses? Do we use some kind of nano-particles that will allow us to get whatever our therapy is to the right place at the right time without a lot of toxicity?

Fortunately, that's the same issue a lot of nervous systems diseases have. So we could certainly help them but they can help us as well; whether it's Alzheimer's, Parkinson's, whatever, they have the same issue. They're trying to get a therapy into the nervous system without causing a lot of toxicity. So I think that those fields will advance as well.

Now,~~So the biggest thing is that there's new methodologies but also the genetics has been successful. They found all these genes, they've given us all these ideas, and now~~ it's about working the ideas through the translational system, trying them in cell models and animal models then start getting ideas for what you can try in people.

**Allen:** This is all very encouraging, Craig. Thanks for taking the time to talk with me today.

**Craig:** Your welcome, Allen. Any time.

*Allen Bernard is a former SPF board member whose daughter was diagnosed with SPG3A in 2006. This article was reviewed for accuracy by Dr. Blackstone.*